

## **REMARKS**

### **Status of Claims**

To advance prosecution, claim 4 has been canceled; and claim 1 has been amended to incorporate the limitations of claim 4. No new matter has been added.

Claims 1 and 2 have been amended to clarify the claim language. Support for this amendment may be found in the specification, for example, in paragraph [0141] of the patent application publication (US 2008/0119424 A1).

Claims 1, 2, 13, and 14-17 currently are pending.

Applicants respectfully request favorable consideration of the pending claims.

### **35 U.S.C. 112, first paragraph, enablement rejection**

The Examiner maintained the rejection of claims 1-4 for reasons of record.

#### **The Examiner's response to Applicants' arguments filed 6/4/2010**

The Examiner withdrew the scope of enablement rejection with respect to the lack of enablement for the broad genus of inhibitors previously claimed in view of the claim amendments adding known classes of HDAC inhibitors.

The Examiner did not find Applicants arguments persuasive with respect to the lack of enablement for a method of treating melanoma, acute leukemia, chronic leukemia, non-small-cell lung carcinoma, head cancer, neck cancer, renal carcinoma, and breast cancer.

The Examiner conceded that that the specification does provide guidance for a method of decreasing A375 melanoma cell proliferation in vitro using an siRNA targeted to a gene encoding PRAME wherein the cells were cultured with an HDAC inhibitor.

As for leukemic cells, the Examiner contended that the prior art is not predictive of method of treating said tumors using an siRNA inhibitor of PRAME and an inhibitor of HDAC. The Examiner contended that (i) Tajeddine found that overexpression of PRAME in cultured leukemic cells were responsible for a slower proliferation rate of said cells and (ii) Tajeddine demonstrates that nude mice injected with siRNA PRAME leukemic cells grew tumors significantly faster than cells that did not have PRAME down-regulated; and (iii) at the time of filing, down-regulating PRAME using siRNA increased the tumorigenicity of leukemic cells..

As for breast cancer cells, the Examiner contended that the post-filed reference Doolan (i) states that prior to Doolan, the prognostic import and prevalence of PRAME expression had not been investigated; (ii) found that PRAME expression correlate with an unfavorable outcome; and (iii) does not provide any evidence of methods of treatment of PRAME such that a decrease of expression of PRAME along with treatment of an HDAC inhibitor provided treatments for breast cancer.

The Examiner further contended that the instant specification does not provide a correlation between treatment effects in a melanoma cell with treatment effects in, for example, a leukemic or breast cell, such that the skilled artisan would know that inhibition of PRAME expression would cause apoptosis in the claimed tumor types just as demonstrated in melanoma cells. The Examiner moreover contended that without this correlation or guidance in the specification on treating any of these tumor types and given it has been shown in the art that PRAME inhibition appears to have the apposite effect of increasing tumorigenicity in some cancers, the skilled artisan would have to practice a substantial amount of undue experimentation to practice the invention.

#### **Applicants' response**

In order to advance prosecution, Applicants have amended independent claim 1 to recite a method of treatment of a tumour which comprises administering to a subject in need of treatment an effective amount of an inhibitor of PRAME, in combination with a

second agent selected from the group of an inhibitor of HDAC (an HDCAi) and a retinoid, said inhibitor of PRAME being an RNA interference (RNAi)-based inhibitor; said inhibitor of HDAC being selected from the group consisting of trichostatin A (TSA), and PXD, 101; wherein said tumour overexpresses PRReferentially expressed Antigen in MElanoma (PRAME), and wherein said tumour is a melanoma.

Applicants reserve the right to file a divisional application directed to subject matter that is not included in the amended claims.

Applicants urge that the specification provides guidance for a method of decreasing melanoma cell proliferation using an siRNA targeted to a gene encoding PRAME. At the time the invention was made, a skilled artisan in this field would be able to read the specification and follow the guidance of the exemplified embodiments and the knowledge in the art to make and use the claimed method. The in vitro experiments using cell lines B16 (mouse melanoma), FM6 (a human HAGE-positive melanoma cell line), SK23 (human melanoma), A375 (human amelanotic melanoma cell line), and in vivo human melanoma xenograft model disclosed in the specification collectively constitute a working example, since those examples correlate with a disclosed or claimed method invention. See MPEP 2164.02. Each of these cell lines originated from actual specific melanoma tumors.

It is well-established that U.S. Patent law does not demand that “human testing occur within the confines of PTO proceedings.” *In re Brana*, 51 F3d 1560 (Fed. Cir. 1995 ) (recognizing that “[t]esting for the full safety and effectiveness” of a drug candidate “is more properly left to the Food and Drug Administration, (FDA)”). Moreover, Applicants urge that the described in vitro and in vivo results with the above-referenced cell lines are predictive for human therapy because “usefulness in patent inventions necessarily include the expectation of further research and development” [*Id.* at 1568].

Since the disclosure complies with the requirements of 35 U.S.C. 112 para. 1, Applicants respectfully request that this ground for rejection be withdrawn.

Since there is no prior art that teaches or suggests the claimed invention, Applicant respectfully requests that the Examiner withdraw all objections to and rejections of the present invention.

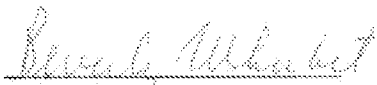
Applicant urges that this application is now in condition for allowance and earnestly solicits early and favorable action by the Examiner. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is respectfully urged to telephone the undersigned at 973-360-7934. The undersigned also may be contacted via e-mail at lubitb@gtlaw.com.

#### AUTHORIZATION

The Commissioner hereby is authorized to charge any fees, including the appropriate fee for a submission of a terminal disclaimer by a small entity, which may be required, or credit any overpayment to Deposit Account 501561.

Respectfully submitted,  
For Greenberg Traurig  
By

Date: 9/21/10

  
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